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# The Course of Adverse Effects of Nortriptyline and Venlafaxine in Elderly Patients with Major Depression

Rob M. Kok, PhD,\* Marja Aartsen, PhD,<sup>†</sup> Willem A. Nolen, PhD,<sup>‡</sup> and Thea J. Heeren, PhD<sup>§</sup>

**OBJECTIVES:** To evaluate tolerability and course of adverse effects of antidepressants in elderly patients and to study the association between number and severity of adverse effects and age, physical comorbidity, antidepressant dose, and depression severity.

**DESIGN:** Double-blind, randomized controlled trial followed by an open treatment phase of 3 years.

**SETTING:** Psychiatric hospital in the Netherlands.

**PARTICIPANTS:** Eighty-one elderly depressed inpatients.

**INTERVENTION:** Patients were treated with venlafaxine or nortriptyline.

**MEASUREMENTS:** Frequency and severity of 43 individual adverse effects were assessed using the Symptom, Sign, Side-Effect Checklist. Severity of depression was assessed using the Montgomery Åsberg Depression Rating Scale.

**RESULTS:** Both antidepressants were tolerated well, with no differences in clinical effectiveness, and most adverse effects decreased with time. The number and severity of adverse effects was not related to age or physical comorbidities. There was a significant relationship between the severity of depression and the severity of adverse effects, although the relationship between the dose of the antidepressant and the severity of the adverse effects was of only borderline statistical significance.

**CONCLUSION:** Elderly patients tolerated venlafaxine and nortriptyline well, and most adverse effects decreased with time as the depression improved. Age and physical comorbidities were not related to number and severity of adverse effects. *J Am Geriatr Soc* 57:2112–2117, 2009.

**Key words:** elderly; antidepressants; adverse effects; randomized controlled trial

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The short-term efficacy and safety of antidepressants in elderly people have been established in many randomized controlled trials (RCTs), reviews, and meta-analyses,<sup>1–4</sup> but many elderly patients with depression do not receive adequate treatment with antidepressants. A recent retrospective study of 12,130 new antidepressant users aged 65 and older found that 34.8% of these patients were taking suboptimal doses of antidepressants.<sup>5</sup> Fear of adverse effects when using higher doses may be an important reason for using such suboptimal treatment regimes. Elderly patients with depression are particularly prone to adverse effects as a result of age-associated changes in pharmacokinetics and pharmacodynamics, drug interactions, and the presence of comorbid physical disorders. In a recent meta-analysis of 37 RCTs comparing tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) in elderly people, it was recognized that recipients of TCAs had not only had a greater withdrawal rate but that this was also specifically due to adverse effects.<sup>6</sup>

The authors feel that more patients might be willing to continue their treatment with antidepressants if practitioners were able to inform patients about the prognosis of adverse effects over time. Therefore, it is important to be able to predict the likely course of (specific) adverse effects and to have knowledge about the influence of dose increase on the severity of adverse effects. Only two studies<sup>7,8</sup> have addressed the longitudinal outcome and course of adverse effects in younger adult patients and only three such studies<sup>9–11</sup> in elderly patients. All of these studies found that adverse effects decreased in frequency over time and that total adverse effect scores were related primarily to residual depression rather than to treatment with antidepressants. None of these studies addressed the influence of age, physical comorbidity, or antidepressant dose on adverse effects. To the best of the authors' knowledge, no double-blind study in elderly people has addressed the course of adverse effects during the acute treatment of depression.

A randomized, double-blind trial lasting 12 weeks compared the effect of nortriptyline and venlafaxine in elderly depressed patients.<sup>12</sup> All patients were asked to participate in an open-treatment phase for a maximum of 3 years. The questions addressed were: Is there a difference in

tolerability of both antidepressants? What is the course of adverse effects? and What is the relationship between the number and severity of adverse effects and age, physical comorbidity, antidepressant dose, and depression severity.

The hypothesis was that venlafaxine would be better tolerated than nortriptyline and that only a few adverse effects would persist during continued treatment. The hypothesis was also that the number and severity of adverse effects would be related to age, physical comorbidity, dose, and depression severity.

## METHODS

### Patients

A double-blind, randomized 12-week parallel-group trial was conducted in inpatients aged 60 and older with depression. Patients were enrolled if they met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for major depression (single or recurrent episode) and had a score of at least 20 on the Montgomery-Åsberg Depression Rating Scale (MADRS; normal range 0–9).<sup>13</sup> Patients were excluded if they met DSM-IV criteria for dementia or had a Mini-Mental State Examination (MMSE; normal range 24–30)<sup>14</sup> score of less than 15, if there was an absolute contraindication to the study medication (e.g., a recent myocardial infarction), or if they had already been treated unsuccessfully for the present episode with venlafaxine ( $\geq 4$  weeks,  $\geq 75$  mg) or with a TCA including nortriptyline ( $\geq 4$  weeks, serum level within therapeutic range).

Details about the flexible dosing schedule of venlafaxine and nortriptyline, the use of adjunctive medication, and the efficacy results have been published elsewhere.<sup>12</sup> Written informed consent was obtained from all patients, or in case of lack of capacity to consent to the trial, consent was obtained from their legal representative. The ethics committee of the Altrecht Institute of Mental Health Care (Zeist, the Netherlands) approved the trial, which was conducted according to the Declaration of Helsinki.

After the initial, double-blind phase, patients were asked to participate in an open study with a follow-up duration of 3 years. Decisions in the open-treatment phase about stopping the antidepressant in case of severe adverse effects or if a patient was in sustained remission were made at the attending physician's discretion.

### Study Assessment

During the double-blind phase, patients were assessed at Weeks 1, 3, 5, 7, 9, and 12. During the open-treatment phase, assessments were done at 6, 9, 12, 24, and 36 months after the start of the double-blind phase.

Antidepressant safety was assessed at all visits with the Symptom, Sign, Side-Effect Checklist (SES)<sup>15</sup> evaluating the presence and severity (rated as 1 = mild, 2 = moderate, 3 = severe) of 43 symptoms or adverse effects. Any symptom present at baseline that had not increased in severity since start of the study medication was not rated as an adverse effect. After each visit, the global burden of adverse effects was calculated by summing the SES severity scores of all individual adverse effects.

The primary tolerability outcome criterion was the percentage of patients dropping out as a result of adverse events during the double-blind treatment phase. Taking into consideration a 22.9% rate of drop out in the nortriptyline group, as found in patients using a TCA according to a recent review,<sup>6</sup> and using an alpha of 0.05 and a power of 0.8, 247 patients would have to be included in each group to find a difference between nortriptyline and venlafaxine of 10% in the proportion of patients dropping out.

The first author made all safety assessments. Severity of depression was evaluated at all visits using the MADRS. Severity and disability resulting from physical illnesses were recorded according to a previously developed method.<sup>16</sup>

### Statistical Analysis

Cross-sectional analysis of the progression of the number and severity of adverse effects during the 3 years of treatment were analyzed using conventional statistical techniques (Student *t*-test, chi-square ( $\chi^2$ ), Pearson correlation). In addition, longitudinal data analyses were performed using latent growth models (LGMs).<sup>17,18</sup> A LGM is a specific type of structural equation model that gives an adequate description of the amount of change observed because it takes into account the lack of reliability of the measurements and the nonlinearity of the trajectories of change.<sup>19</sup> In this study, a LGM was used to explicitly test the nonlinear course of adverse events by comparing the goodness-of-fit statistics (the comparative fit index (CFI) and the root mean square error of approximation (RMSEA)) of two nested models. Cross-domain LGM is an extension of the LGM in the sense that, next to a description in the course of adverse effects, relationships between patterns of change on different variables can also be estimated.

The conventional analyses were conducted using SPSS 14.0 for Windows (SPSS, Inc., Chicago, IL) using two-sided tests, and test statistics are presented with *P*-values. To correct for multiple testing,  $P \leq .01$  was considered significant for all post hoc analyses and  $P = .05$  to  $.01$  was considered of borderline significance. The analyses on the longitudinal data (LGM) were performed using *Mplus* (Muthén & Muthén, Los Angeles, CA).

## RESULTS

The sample consisted of 81 patients who started the double-blind RCT. Baseline demographic and clinical variables are presented in Table 1. The results of the double-blind treatment phase are first presented; only limited data on the 3 years of follow-up are presented, because it was desired not to mix results from a double-blind treatment phase with a predetermined dosing schedule with results from the 3 years of nonblind observations in which doses could be changed according to the psychiatrists' discretion. In addition, the majority of patients stopped their antidepressant during the 3 years of open treatment, limiting the power of statistical analysis.

The mean dose and standard deviation at the end of the RCT in patients using venlafaxine was  $156 \pm 71$  mg/d; the mean dose of nortriptyline was  $94.5 \pm 30.4$  mg/d.

The first research question concerned a possible difference in tolerability between both antidepressants. Three

**Table 1. Baseline Characteristics (Intention-to-Treat Group)**

Characteristic	Venlafaxine (n = 40)	Nortriptyline (n = 41)	P-Value
Age, mean $\pm$ SD	71.6 $\pm$ 6.8	72.8 $\pm$ 8.4	.48
Female, n (%)	27 (67.5)	32 (78.1)	.29
Duration current episode, months mean $\pm$ SD	6.2 $\pm$ 5.1	4.7 $\pm$ 3.4	.20
Montgomery Åsberg Depression Rating Scale score, mean $\pm$ SD (normal range 0–9)	32.9 $\pm$ 6.4	32.9 $\pm$ 6.0	>.99
Patients taking concomitant psychiatric medications, n (%)	33 (82.5)	36 (87.8)	.50
Number of concomitant psychiatric medications, mean $\pm$ SD	1.4 $\pm$ 0.9	1.7 $\pm$ 0.9	.40
Concomitant number of physical illnesses, mean $\pm$ SD	6.3 $\pm$ 2.4	6.3 $\pm$ 2.5	.97
Concomitant number of somatic medications, mean $\pm$ SD	3.0 $\pm$ 2.2	3.4 $\pm$ 3.0	.68

SD = standard deviation.

patients treated with nortriptyline and two treated with venlafaxine stopped it because of adverse effects. The only adverse effect with statistical significance in prevalence was dry mouth, which was more prevalent in patients taking nortriptyline (87.8%, vs 50% of patients taking venlafaxine;  $\chi^2 = 13.6$ , degrees of freedom ( $df$ ) = 1,  $P < .001$ ).

Table 2 presents the number of at least moderately severe adverse effects per patient at each visit. Table 3 presents the severity of the adverse effects at each visit. No statistically significant difference in adverse effects between the two drugs could be demonstrated at any visit. Because it was more likely that patients with more-severe adverse effects would drop out of the trial, the analyses in Tables 2 and 3 were repeated with a completer's analysis and with a last observation carried forward technique, which yielded the same results.

The second research question concerned the course of adverse events. Table 2 suggest an initial increase followed by a decrease in the number of side effects in both patient groups. The LGM confirmed this nonlinear pattern. The fit of the model in which nonlinear change was modeled was excellent ( $\chi^2 = 10.60$ ,  $df = 12$ ,  $P = .39$ , CFI = 1.00, RMSEA = 0.03), which is significantly better than the fit of the model with linear change ( $\chi^2 = 20.00$ ,  $df = 12$ ,  $P = .07$ , CFI = 0.96, RMSEA = 0.09).

The third research question concerned the relationship between the number and severity of adverse effects and several potential determinants.

### Age

There was no statistically significant relationship between age and number or severity of adverse effects.

### Physical Illness

No significant correlation could be demonstrated between the number or severity of the physical illnesses and the number or severity of adverse effects (correlation coefficient ( $r$ ) = 0.00–0.25, all except one  $P$ -value > .05).

### Dose

The mean daily dose of venlafaxine increased from 75 mg at Week 1 to a maximum of 162  $\pm$  69 mg at Week 9, and the dose of nortriptyline increased from 75 mg at Week 1 to a maximum of 131  $\pm$  63 at Week 9. There was no statistically significant cross-sectional correlation between dose and number of adverse effects (Pearson  $r = 0.07$ –0.22; all  $P$ -values > .05), although the cross-sectional correlation between dose of antidepressant and severity of adverse effects was of borderline significance ( $r = 0.29$ –0.38, all  $P$ -values < .05 and one  $P$ -value < .01).

### Depression Severity

The cross-sectional correlation between MADRS score and number of adverse effects was of borderline significance in all except the first visit after start of the medication ( $r = 0.25$ –0.36, with all  $P$ -values < .05 and only one  $P$ -value < .01). To detect whether changes in MADRS

**Table 2. Number of at Least Moderately Severe Adverse Effects per Patient in Elderly Patients with Major Depression**

Visit	Week	Observed Patients, n	Mean $\pm$ Standard Deviation		P-Value
			Venlafaxine	Nortriptyline	
2	1	81	4.0 $\pm$ 4.4	3.4 $\pm$ 3.0	.48
3	3	79	3.8 $\pm$ 3.4	4.2 $\pm$ 2.9	.56
4	5	75	4.7 $\pm$ 3.9	4.9 $\pm$ 3.0	.75
5	7	74	4.5 $\pm$ 3.6	5.0 $\pm$ 4.2	.63
6	9	68	4.6 $\pm$ 4.6	4.5 $\pm$ 3.2	.86
7	12	62	2.4 $\pm$ 2.7	3.5 $\pm$ 3.5	.14

**Table 3. Total Severity of Adverse Effects in Elderly Patients with Major Depression (Mean  $\pm$  Standard Deviation)**

Visit	Week	Observed Patients, n	Mean $\pm$ Standard Deviation		P-Value
			Venlafaxine	Nortriptyline	
2	1	81	18.3 $\pm$ 8.6	16.8 $\pm$ 6.8	.38
3	3	79	15.0 $\pm$ 8.3	15.4 $\pm$ 7.6	.83
4	5	75	16.2 $\pm$ 8.7	15.9 $\pm$ 7.0	.88
5	7	74	14.3 $\pm$ 9.2	13.8 $\pm$ 7.7	.80
6	9	68	12.7 $\pm$ 8.4	12.9 $\pm$ 6.5	.94
7	12	62	13.5 $\pm$ 9.5	11.9 $\pm$ 6.5	.46

score were correlated with changes in the number of adverse effects, a cross-domain LGM was applied. The fit of the model was good ( $\chi^2 = 60.82$ ,  $df = 51$ ,  $P = .16$ , CFI = 0.98, RMSEA = 0.05), and a significant covariation was found between change in MADRS score and change in number of adverse effects (covariance = 0.10, 95% confidence interval = 0.03–0.17).

MADRS score was also significantly correlated cross-sectionally with severity of adverse effects ( $r = 0.52$ – $0.71$ , all  $P$ -values  $< .01$ ). An estimation of the longitudinal correlation between change in MADRS score and change in severity of side effects failed, partly because of the absence of a relationship between change of severity and time.

### Follow-Up

During the 3 years of open treatment, three patients stopped using venlafaxine, and three patients stopped using nortriptyline because of adverse effects. Their depression was in remission at the time of dropout. A survival analysis including the double-blind and the open-treatment phases could not demonstrate a difference between the antidepressants in dropouts due to side effects (Wald 0.345,  $df = 1$ ,  $P = .56$ ).

After 3 years of observation, 22 patients who started with nortriptyline continued with it, whereas only four of the patients who started with venlafaxine were still taking it. This difference in attrition rate is the result of a higher number of patients stopping venlafaxine because of a lack of efficacy, not adverse events.

The number and severity of all adverse events decreased gradually during the follow-up phase in both antidepressants, with no statistically significant difference between venlafaxine and nortriptyline at any visit. Dry mouth was the most frequent adverse effect of nortriptyline throughout the open-treatment phase, with a prevalence of 43% after 3 years (9/22 patients). Other anticholinergic adverse events persisted in a much smaller minority of patients using nortriptyline (constipation in 2 patients and impaired urination in 1 patient). In patients taking venlafaxine, the most prevalent adverse effect in the open-treatment phase was weight gain (8/16 patients at 6 months and 4/9 patients at 9 months, in later visits the number was too small for analysis).

### DISCUSSION

There are few trials reporting the long-term tolerance of adverse effects of antidepressants in elderly people, whereas medication is often taken for longer periods of time. In the current study, most patients tolerated venlafaxine and nortriptyline well in the double-blind phase and the open-treatment phase. The primary outcome criterion was the percentage of patients dropping out as a result of adverse events during the double-blind treatment phase; a statistically significant difference could not be demonstrated between venlafaxine and nortriptyline. In addition, after 3 years of open treatment, no difference in tolerability between nortriptyline (6 dropouts because of adverse effects) and venlafaxine (5 dropouts because of adverse effects) could be demonstrated. These results are in concordance

with the good long-term tolerability of nortriptyline as shown in double-blind RCTs of maintenance treatment with this TCA in elderly patients with depression in remission.<sup>20,21</sup> Patients who entered the open-treatment phase were by definition a cohort that had been proven to tolerate the study drug for at least 12 weeks during the double-blind phase.

The dropout rate due to adverse effects in the double-blind phase of the study (6.2%) was significantly lower than the withdrawal rate of 22.9% due to adverse effects with TCAs and of 17.3% with SSRIs in patients included in a recent meta-analysis<sup>6</sup> of adverse effects in elderly patients with depression ( $P = .003$  and  $.02$ , respectively). Perhaps the frequent and systematic assessment of the presence and severity of possible adverse effects contributed to the low dropout rate. In the authors' experience, most patients are willing to continue the antidepressant after discussing the advantages of continuing treatment, the delay in response due to a switch to another antidepressant, and the possibility of supportive countermeasures. Moreover, all of the patients started as inpatients, and only a small minority were discharged before a response was achieved, in contrast to the outpatients in the majority of studies included in the meta-analysis. Therefore, the surprisingly low dropout rate may also reflect that the nursing staff encourages patients to continue treatment in inpatients wards.

The course of adverse effects was the second research question, and this is the first double-blind study that presents the course of adverse effects in more detail during the acute phase of treatment in elderly patients. An interesting and new finding is the initial increase followed by a decrease in number of adverse effects. An open study in elderly patients found a decline in frequency of somatic complaints during 7 consecutive months of treatment with nortriptyline.<sup>9</sup> In the only adult study that the authors are aware of to compare these results with, an immediate and constant, although not linear, decline in number of adverse events in each consecutive visit was found.<sup>7</sup> A different dosing schedule may explain this different course; the previous study used a fixed dose regimen and the current study used a flexible dose regimen with an increase in mean dose during the first weeks of treatment.

After 2 to 3 years of treatment, most patients reported one to two adverse effects, compared with four to five adverse effects at maximum during the double-blind treatment phase, which confirms the second research hypothesis. Because only a few patients dropped out because of adverse events, the early dropout of the patients suffering from the most-severe adverse events probably does not explain the results. Dry mouth was the most persistent adverse effect in this study population, which is in accordance with a previous report in elderly people.<sup>11</sup>

This may prove that better explanation to patients of the fact that adverse events might decrease in number and severity with time might influence outcome of antidepressant use in this patient group.

The third research question concerned possible determinants of tolerability. To the best of the authors' knowledge, this study is the first RCT in adult or elderly patients that has explored the relationship between adverse effects and age, physical comorbidity, and antidepressant dose. Age and physical comorbidity were associated neither with

the number nor with the severity of adverse effects. This is in keeping with results of another study in elderly patients with depression, in which no relationship was found between adverse effects and physical comorbidities.<sup>22</sup> This suggests that age and (age-associated) physical illnesses may not have as a great influence on tolerability as often thought.

No relationship was found between the number of adverse effects and the dose of antidepressants. There was a low correlation, although of borderline statistical significance, between the severity of adverse effects and antidepressant dose. Because there was only a limited variation in the prescribed dosages, especially in patients treated with venlafaxine, these results need replication before more-definitive conclusions can be drawn. These data can be compared only with the finding that there was no significant correlation between the global burden of adverse effects and the blood levels of nortriptyline in a nonblind study of elderly patients.<sup>9</sup>

Depression severity was associated with the number, although with borderline statistical significance, and severity of adverse effects. This is in concordance with an earlier report in elderly patients.<sup>10</sup> This is the first study in elderly people to replicate the moderate but significantly correlation found between decrease in reported adverse events and decrease in severity of depression in adult patients.<sup>7</sup>

If confirmed, the lack of association between adverse effects and antidepressant dose suggests that clinicians should be reluctant to reduce antidepressant dose to improve adverse effects. The significant association between adverse effects and depression severity is an additional argument for clinicians to convince patients not to lower an adequate dose of antidepressant, because a sub-optimal treatment strategy will result in a lower chance of remission.

The number of patients in this study may have limited its power, and according to the power analysis, the possibility of a type II error cannot be excluded, although this was the case with other similar studies too. Nevertheless, there was an increasing imbalance between the number of patients using nortriptyline and venlafaxine during the open-treatment phase, although this was due to differences in efficacy and not in tolerability. Another limitation is the use of nortriptyline and venlafaxine, neither of which is a first-line antidepressant for use in elderly people. Both antidepressants were chosen because it was anticipated that the subjects, being inpatients, would suffer from more-severe depression, often with psychotic features. The Expert Consensus Guideline on pharmacotherapy of depressive disorders in older patients suggests that both antidepressants are adequate treatment strategies in these subgroups of patients with depression.<sup>23</sup>

## CONCLUSION

These data support the long-term tolerability of nortriptyline and venlafaxine in elderly patients who need maintenance treatment and suggest that adverse events diminish in frequency in most of these patients. Nevertheless, it remains difficult to determine the origin of somatic complaints during treatment with antidepressants.

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**Conflict of Interest:** The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper. Dr. Kok has received research grants from Wyeth and Lundbeck and has received speaker's honoraria from GlaxoSmithKline, Lundbeck, Pfizer, and Wyeth. Dr. Nolen has received research grants from Astra Zeneca, GlaxoSmithKline, and Wyeth; has served as consultant for Astra Zeneca, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, and Pfizer; and has received speaker's honoraria from Astra Zeneca, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Organon, and Pfizer. Dr. Heeren has received speaker's honoraria from Eli Lilly and Lundbeck. This study was in part supported by a grant from Wyeth (100186).

**Author Contributions:** Dr. Kok: all aspects of the study. Ms. Aartsen: longitudinal data analysis and interpretation, preparing the manuscript. Dr. Nolen: preparing the manuscript. Dr. Heeren: study design and preparing the manuscript.

**Sponsor's Role:** None.

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